Side Effects of α-Blocker Use: Retrograde Ejaculation

Steven A. Kaplan, MD

Institute for Bladder and Prostate Health, Weill Cornell Medical College of Cornell University, New York, NY

There are currently 5 α-blockers that are approved by the US Food and Drug Administration to treat lower urinary tract symptoms (LUTS). The American Urological Association guidelines committee believes that all α-blockers are equally effective. However, α-blockers differ in their likelihood of causing abnormal ejaculation. This article discusses the effects on ejaculatory function, and specifically retrograde ejaculation, of the currently available α-blockers being used to treat men with LUTS due to benign prostatic hyperplasia.
[Rev Urol. *2009;11(suppl 1):S14–S18 doi: 10.3909/riu11S1S0001*]

Key words: α-Blockade • Benign prostatic hyperplasia • Lower urinary tract symptoms • Retrograde ejaculation

In the 1980s, the recognition by Lepor and colleagues that prostatic smooth muscle tension was mediated by α_1-adrenoceptors led to the development of α-blockade as a treatment of lower urinary tract symptoms (LUTS).[1] This dynamic component of prostatic obstruction accounts for approximately 40% of outflow obstruction due to benign prostatic hyperplasia (BPH).[2] There are currently 5 α-blockers that are US Food and Drug Administration (FDA) approved to treat LUTS: doxazosin, terazosin, tamsulosin, alfuzosin, and silodosin. The American Urological Association (AUA) guidelines committee believes that all α-blockers, regardless of their selectivity for α_1-receptor subtypes, including α_{1A}-, α_{1B}- and α_{1D}-receptors, are equally effective, causing on average a 4- to 6-point improvement in the AUA symptom score, which most patients perceive as a meaningful change.[3] The AUA statement was published in 2006, prior to silodosin's approval by the FDA.

Adverse side effects commonly reported with different α_1-blockers include dizziness, headache, asthenia, postural hypotension, rhinitis, and sexual dysfunction.[4] Specifically, sexual dysfunction has been related to changes in ejaculation (either retrograde or diminished ejaculation). Moreover, α-blockers differ in their likelihood of causing abnormal ejaculation.[5] In controlled clinical trials, the percentage of patients treated with the α_{1A}-selective α-blocker tamsulosin who reported abnormal ejaculation varied between 4% and 26%, depending on dose and study duration.[6,7] In a long-term, open-label extension study, 30% of patients treated with tamsulosin reported abnormal ejaculation.[8] In contrast, incidences of abnormal ejaculation related to the use of nonselective α-blockers, such as doxazosin, terazosin, or alfuzosin, generally were lower than 1.5%.[3]

Lower Urinary Tract Symptoms and Sexual Function

LUTS is associated with significant impairment in sexual activity, satisfaction with sexual relationships, and quality of life.[9] Therefore, it is not surprising that a significant number of sexually active men with LUTS/BPH consult physicians for erectile dysfunction and other genitourinary difficulties. Although sexual activity normally diminishes with age, impaired sexual performance remains an undesirable side effect of BPH, and treatment often produces significant clinical improvement and symptom reduction. Clinical evaluations have now confirmed studies in preclinical models showing that blockade of α-adrenergic activity can improve sexual function. In 1 study, patients with erectile dysfunction treated with intracavernosal alprostadil injection showed a significant improvement in sexual function when they also received an oral α_1-adrenergic blocker ($P < .01$).[10]

In the setting of treatment of LUTS/BPH, Höfner and colleagues[11] demonstrated through a sexual function score (determined from a lifestyle questionnaire) that, when compared with placebo, treatment with tamsulosin actually improved total sexual function scores. This finding is supported by the results of a validated BPH-specific health-related quality-of-life questionnaire administered to patients treated with alfuzosin. Treatment with this agent was associated with significant improvements in perceived sexuality at 12 months ($P < .0001$).[12]

Abnormal Ejaculation

As described previously, abnormal ejaculation is a class effect of treatment with α_1-adrenergic receptor blockers, although it is rarely serious enough to prompt patients to withdraw from treatment (the risk of ejaculation disorders due to α-blocker therapy for BPH is much lower than that from surgical intervention for BPH).

LUTS is associated with significant impairment in sexual activity, satisfaction with sexual relationships, and quality of life.

In the past, we have interpreted changes in ejaculatory function as an adverse event. In contrast, some have postulated that changes in ejaculation were a proxy for efficacy. That is, the greater the incidence of ejaculatory changes, the more likely a patient was undergoing a medical transurethral resection of the prostate (TURP). However, to date, this hypothesis has not been supported by robust clinical data. In part, this has been due to lack of uniform definition of ejaculatory function and dysfunction.

Some have postulated that changes in ejaculation were a proxy for efficacy.

According to the *Medical Dictionary for Regulatory Activities*, the definition of retrograde ejaculation (RE) includes a broad spectrum of patient-reported events of abnormal ejaculation, including absence of seminal emission, reduced ejaculate volume, and reduced ejaculation force. We assume that relaxation of the bladder neck muscle secondary to α_{1A}-receptor blockade leads to backflow of seminal fluid from the prostatic urethra into the bladder.

Tamsulosin and Alfuzosin

In a seminal study, Hellstrom and coworkers[13] examined the effects of tamsulosin and the nonselective α-blocker alfuzosin on ejaculatory function in healthy volunteers and found that tamsulosin 0.8 mg/day caused markedly reduced ejaculate volume in 90% of patients and anejaculation in 35% of patients. However, analysis of postclimactic urine samples showed no increase in sperm counts, suggesting that RE did not occur. In addition, others have theorized that α_{1A}-selective α-blockers may result in reduced or absent seminal emission via inhibition of smooth muscle contraction.[14]

Silodosin

The most recent FDA-approved α-blocker, silodosin, has unique receptor subtype and tissue selectivity.[15] Silodosin is 162 times more selective for α_{1A} than for α_{1B}, and is approximately 55 times more selective for α_{1A} than for α_{1D}.[16] Consistent with other α-blockers, there is significantly improved BPH-related LUTS and peak

urinary flow rates (Q_{max}).[17] However, consistent with the findings of earlier clinical studies of silodosin in Japanese patients,[18] high incidences of abnormal ejaculation were reported. Specifically, 28% of silodosin-treated patients in the 2 US studies reported abnormal ejaculation (classified as RE), as did 22.3% of silodosin-treated patients in the Japanese study.[18]

Are the efficacy of silodosin and its propensity to cause abnormal ejaculation both attributable to the selective blockade of α_{1A}-receptors? If so, do men who experience abnormal ejaculation achieve greater symptom relief than those with no ejaculatory disturbances? Recently, post hoc analyses of data from 2 placebo-controlled, US phase III trials of silodosin examined the relationship between the absence or presence of RE and clinical efficacy.[19]

Men 50 years or older with International Prostate Symptom Scores (IPSS) of at least 13 and peak urinary flow rates of 4 to 15 mL/s received placebo or silodosin, 8 mg, once daily for 12 weeks. Silodosin-treated patients were stratified by absence or presence of RE. Baseline characteristics and efficacy data were stratified by ejaculation status among patients treated with silodosin (ie, absence [RE−] or presence [RE+] of RE). To evaluate the relationship between ejaculation status and silodosin efficacy, 2 responder analyses were performed. For the first analysis, a patient was considered a responder if he experienced a 30% improvement in both IPSS score and Q_{max} from baseline to the last assessment. For the second analysis, a patient was considered a responder if he experienced improvement in Q_{max} of at least 3 mL/s and in IPSS total score of 3 points or greater. Analysis groups were compared using analysis of covariance (for change from baseline) and responder analyses.

Table 1
Incidence of Retrograde Ejaculation in 2 Phase III Studies of Silodosin

	Study SI04009 (Patients, n)	Study SI04010 (Patients, n)	Combined
Placebo	228	229	457
Silodosin	233	233	466
Presence of RE (%)	68 (29)	63 (27)	131 (28)
Absence of RE (%)	165 (71)	170 (73)	335 (72)

RE, retrograde ejaculation.

In the 466 patients receiving silodosin, 131 (28%) reported RE and 335 (72%) did not; 4 of 457 patients receiving placebo (0.9%) reported RE. Most RE events in silodosin-treated patients (110/134; 82%) were reported as orgasm with absence of seminal emission (Table 1). Of note, the mean age of patients in the silodosin RE+ group was significantly lower than that of patients in the silodosin RE− group. Of 150 patients younger than 60 years who were treated with silodosin, 69 (46.0%) reported RE and 7 (4.7%) discontinued because of RE. Of 191 patients aged 60 to 70 years, 48 (25.1%) reported RE and 6 (3.1%) discontinued, and of 125 patients older than 70 years, 14 (11.2%) reported RE and none discontinued.

Both silodosin RE groups showed significant improvement in IPSS, Q_{max}, and quality of life versus placebo ($P < .02$). Moreover, these efficacy parameters were numerically greater in patients with RE than in those without RE, but differences between the silodosin RE+ and RE− groups were not statistically significant.

For patients with RE, the odds of achieving improvement of both 3 points or more in IPSS and 3 mL/s or greater in Q_{max} by study end were 1.75 times those for patients with no RE ($P = .0127$). A total of 9.2% of patients who received placebo achieved an improvement of at least 30% in both IPSS and Q_{max}. In comparison, 20.9% of patients in the silodosin RE− group and 27.5% in the silodosin RE+ group achieved at least 30% improvement in both IPSS and Q_{max}. In a second responder analysis, total IPSS improved by at least 3 points and Q_{max} by at least 3 mL/s (3 units of improvement); 12.9% of patients receiving placebo compared with 23.0% in the silodosin RE− group and 34.4% in the silodosin RE+ group reached this level of response.

The odds ratios versus placebo of achieving 30% improvement were 2.61 for patients in the silodosin RE− group ($P < .0001$) and 3.74 for patients in the silodosin RE+ group ($P < .0001$). The odds of 30% improvement for patients in the silodosin RE+ group were 1.43 times those for patients in the silodosin RE− group ($P = .1285$). The odds ratios versus placebo of achieving improvement of 3 units were 2.01 ($P < .001$) for patients in the silodosin RE− group and 3.53 ($P < .0001$) for patients in the silodosin RE+ group. The odds of achieving an improvement of 3 units for patients in the silodosin RE+ group were 1.75 times those for patients in the silodosin RE− group, for a statistically significant difference ($P = .0127$) (Table 2).

Table 2
Responder Analysis by RE Versus No RE Based on Percentage or Absolute Improvement in IPSS and Q_{max}

30%/30%	Placebo (457)	No RE (335)	RE (131)
Responder	9.5%	22%	30.6%
OR vs placebo		2.67 $P < .0001$	4.18 $P < .0001$
OR RE vs no RE			1.57 $P = .0714$
3 points/3 mL/s	**Placebo (457)**	**No RE (335)**	**RE (131)**
Responder	13.1	23.7%	34.2%
OR vs placebo		2.05 $P = .0003$	3.45 $P < .0001$
OR RE vs no RE			1.68 $P = .0321$

IPSS, International Prostate Symptom Score; OR, odds ratio; Q_{max}, peak urinary flow rate; RE, retrograde ejaculation.

Data Analysis

A number of important messages can be gleaned from these data. First, age may be a predictive baseline characteristic for the occurrence of silodosin-related abnormal ejaculation. This may be due in part to younger men having a greater likelihood and frequency of sexual activity and therefore being more prone to notice this sequela.

When changes in IPSS and Q_{max} were compared, silodosin-treated patients with RE had numerically greater improvement than those without RE, albeit not statistically significant. Moreover, predefined responses, that is, the proportions of patients with a minimum improvement of 30% in both IPSS and Q_{max}, and the proportions of patients with improvement of at least 3 units in both IPSS and Q_{max}, were greater among those with RE than those without RE.[2] Furthermore, odds ratios indicated that patients with RE were significantly more likely than those without RE to achieve a combination of symptom improvement (IPSS total) by at least 3 points and Q_{max} improvement by at least 3 mL/s.

Could the absence of seminal emission for individual patients with BPH-related symptoms be a sensitive indicator of a positive response to treatment with an α_{1A}-selective α-blocker? Furthermore, could ejaculatory status help to identify men who are particularly sensitive to such a therapy? These data, albeit intriguing, offer only a glimpse into the biologic basis for lesser or greater sensitivity to therapy with α_{1A}-selective α-blockers.

Finally, it should be noted that these post hoc analyses have inherent limitations. Were all patients grouped properly under the term *retrograde ejaculation*? Moreover, given the self-reporting nature of these adverse events, several conditions had to be met for an event of RE to be reported: the patient had to be sexually active, had to remember the event until the next clinical visit, and had to consider the event worth reporting. Given the

Main Points

- There are currently 5 α-blockers that are approved by the US Food and Drug Administration (FDA) to treat lower urinary tract symptoms (LUTS). The American Urological Association (AUA) guidelines committee believes that all α-blockers are equally effective, causing on average a 4- to 6-point improvement in the AUA symptom score, which most patients perceive as a meaningful change.
- Adverse side effects commonly reported with different α_1-blockers include dizziness, headache, asthenia, postural hypotension, rhinitis, and sexual dysfunction. Specifically, sexual dysfunction has been related to changes in ejaculation (either retrograde or diminished ejaculation).
- Clinical evaluations have now confirmed studies in preclinical models showing that blockade of α-adrenergic activity can improve sexual function.
- The most recent FDA-approved α-blocker, silodosin, has unique receptor subtype and tissue selectivity. Consistent with other α-blockers, there is significantly improved benign prostatic hyperplasia–related LUTS and peak urinary flow rates (Q_{max}).
- The risk of ejaculation disorders due to α-blocker therapy for BPH is much lower than that from surgical intervention for BPH.

number of patients who experienced RE, this retrospective analysis was too small for the performed analyses to have sufficient statistical power.

Conclusions

The relationship between the causal efficacy of α-blockers (and specifically silodosin) and the occurrence of RE remains to be determined. To more definitively answer this question, prospective studies sufficiently powered to demonstrate significant differences in clinical outcomes depending on the presence or absence of seminal emission are needed. Moreover, uniform, detailed, and validated questionnaires that rigorously address sexual activity and ejaculatory function must be used. Nevertheless, these data represent the first that may suggest a more robust relationship between voiding and sexual function. Moreover, choice of therapies designed to effectuate a better clinical response based on agent used even within a certain drug class will need to be considered in the future. ■

References

1. Lepor H, Gup DI, Baumann M, Shapiro E. Laboratory assessment of terazosin and alpha-1 blockade in prostatic hyperplasia. *Urology*. 1988;32:21-26.
2. Narayan P, Tewari A. Overview of alpha-blocker therapy for benign prostatic hyperplasia. *Urology*. 1998;51(suppl 1):38-45.
3. American Urological Association Practice Guidelines Committee. *Results of the Treatment Outcomes Analyses*. In: Guideline on the Management of Benign Prostatic Hyperplasia (BPH). American Urological Association Education and Research; 2006:1-142. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/ main-reports/bph-management/chapt_3_appendix.pdf. Accessed November 10, 2009.
4. Gillenwater JY, Conn RL, Chrysant SG, et al. Doxazosin for the treatment of benign prostatic hyperplasia in patients with mild to moderate essential hypertension: a double-blind, placebo-controlled, dose-response multicenter study. *J Urol*. 1995;154:110-115.
5. Andersson KE, Gratzke C. Pharmacology of alpha1-adrenoceptor antagonists in the lower urinary tract and central nervous system. *Nat Clin Pract Urol*. 2007;4:368-378.
6. Wilt TJ, Mac DR, Rutks I. Tamsulosin for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2003;CD002081.
7. Lepor H. Long-term evaluation of tamsulosin in benign prostatic hyperplasia: placebo-controlled, double-blind extension of phase III trial. Tamsulosin Investigator Group. *Urology*. 1998;51:901-906.
8. Narayan P, Lepor H. Long-term, open-label, phase III multicenter study of tamsulosin in benign prostatic hyperplasia. *Urology*. 2001;57:466-470.
9. Calais Da Silva F, Marquis P, Deschaseaux P, et al. Relative importance of sexuality and quality of life in patients with prostatic symptoms. Results of an international study. *Eur Urol*. 1997;31:272-280.
10. Kaplan SA, Reis RB, Kohn IJ, et al. Combination therapy using oral alpha-blockers and intracavernosal injection in men with erectile dysfunction. *Urology*. 1998;52:739-743.
11. Höfner K, Claes H, De Reijke TM, et al.; for the European Tamsulosin Study Group. Tamsulosin 0.4 mg once daily: effect on sexual function in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol*. 1999;36:335-341.
12. Lukacs B, Leplège A, Thibault P, et al. Prospective study of men with clinical benign prostatic hyperplasia treated with alfuzosin by general practitioners: 1-year results. *Urology*. 1996;48:731-740.
13. Hellstrom WJ, Sikka SC. Effects of acute treatment with tamsulosin versus alfuzosin on ejaculatory function in normal volunteers. *J Urol*. 2006;176:1529-1533.
14. Michel MC. Alpha1-adrenoceptors and ejaculatory function. *Br J Pharmacol*. 2007;152:289-290.
15. Tatemichi S, Tomiyama Y, Maruyama I, et al. Uroselectivity in male dogs of silodosin (KMD-3213), a novel drug for the obstructive component of benign prostatic hyperplasia. *Neurourol Urodyn*. 2006;25:792-799.
16. Tatemichi S, Kobayashi K, Maezawa A, et al. [Alpha1-adrenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213).] *Yakugaku Zasshi*. 2006;126:209-216.
17. Marks LS, Gittelman MC, Hill LA, et al. Rapid efficacy of the highly selective alpha1A-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. *J Urol*. 2009;181:2634-2640.
18. Kawabe K, Yoshida M, Homma Y. Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. *BJU Int*. 2006;98:1019-1024.
19. Roehrborn CG, Lepor H, Kaplan SA. Retrograde ejaculation induced by silodosin is the result of relaxation of smooth musculature in the male urogenital tracts and is associated with greater urodynamic and symptomatic improvements in men with LUTS secondary to BPH. *J Urol*. 2009;181:694. Abstract 1922.